56. (New) The method of claim 55, wherein the HMG-CoA reductase inhibitor decreases the formation of A-β peptides, increases the clearance of Aβ peptides, regulates the processing of amyloid precursor protein, or reduces plaque maturation in the mammal.

57. (New) The method of claim 55, wherein the HMG-CoA reductase inhibitor is selected from the group consisting of mevastatin, pravastatin, simvastatin, atorvastatin, lovastatin, rivastatin, fluvastatin, and pharmaceutically acceptable salts, isomers and the active metabolite thereof.

58. (New) The method of claim 57, wherein the HMG-CoA reductase inhibitor is lovastatin or lovastatin acid.

59. (New) A method for treating a mammal having an amyloid precursor protein processing disorder comprising administering to said mammal a composition lowering the amount of cholesterol levels in the mammal and altering the processing of amyloid precursor protein which reduces the amount of β amyloid produced.

REMARKS

This is in response to the first Office Action dated July 3, 2001 in the subject application. Claims 1-28 and 33 were under consideration for the purposes of this action pursuant to a restriction requirement and applicants' election of those claims. Applicants have cancelled claims 1-35 and submitted new claims 36-59. New claims 36-43 correspond to original claims 1-8, new claims 44-58 correspond to original claims 14-28 and new claim 59 corresponds to original claim 33. Although these new claims correspond substantially to the original claims, they include certain amendments which

have been made to address issues raised in the instant office action. Original claims 29-32 were withdrawn from consideration and have been cancelled. No new claims directed to the subject matter of original claims 29-32 are presented herein. Applicant respectfully requests reconsideration of the claims as now presented.

Claims 9-16 were objected to under 37 CFR 1.75 (c) as being of improper dependent form for failing to limit the subject matter of a previous claim. Applicants believe that the specific plasma concentration of drug recited in original claims 9-16 further limit the base claim and are therefore in proper dependent form. Nevertheless, applicants have amended these claims (now presented as new claims 44-46) to more clearly refer to the elements of the base claim. Applicants believe that the new claims 44-46 are compliant with the requirements of 37 CFR 1.75(c), and respectfully requests that the objection under 37 CFR 1.75(c) be withdrawn.

Claims 1-28 and 33 were rejected under 35 USC § 112 second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter. Specifically, the Office Action states that the claims 1-28 and 33 are indefinite for failure to define the expression "APP". For each of the identified claims (now presented as new claims 36-59), the expression "APP" has been replaced with "amyloid precursor protein" as defined in the specification.

Applicant appreciates the Examiner's consideration of each of the above-referenced claims as if reciting "amyloid precursor protein", as intended, in order to

expedite prosecution of this application. Applicant believes the newly presented claims are fully compliant with 35 USC § 112. At this time applicant respectfully requests that the rejection under 35 USC § 112, second paragraph, be removed.

Claim 33 stands rejected under 35 USC § 102(b) as being anticipated by Simons et al. The Examiner rejected claim 33 under § 102(b) as anticipated by Simons et al. The Examiner argues that Simons et al. discloses the use of lovastatin to lower cholesterol, and that it is useful in treating a mammal having an APP processing disorder such as Alzheimer's. Applicants respectfully traverse.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Applicants assert that the Examiner has over generalized what is actually taught by Simons. Simons does not teach systemic treatment of a mammal with an APP processing disorder with lovastatin alone. Simons et al. describe treatment of hippocampal neurons in culture (*in vitro*) in the presence of a cocktail comprising 4 μM lovastatin and 0.25 mM mevalonate for 4 days (p. 6461, ¶ 1). Simons further describes a reduction of Aβ only when the lovastatin/mevolonate cocktail is combined with 5 mM methyl-β-cyclodextrin for 5-20 minutes (p. 6461, ¶ 2). Simons does not disclose or teach

the present invention of systemic administration of a therapeutic amount of HMG-CoA reductase inhibitors to a mammal *in vivo*, without co-administration of mevalonate, or methyl-β-cyclodextrin. Accordingly, Simons et al. do not teach the claimed method, and in fact is in contradistinction to the claimed method. In view of this clear differentiation from Simons, et al. the claimed method is outside the four corners of the cited reference and therefore cannot be anticipated by this reference. Therefore Simons et al. cannot anticipate claim 33 of the present invention. Applicants respectfully request the rejection under § 102(b) be withdrawn.

Claims 1-28 and 33 have been rejected under 35 USC § 103(a) as being unpatentable over Scolnick, in view of Sabbagh et al. and May. Applicant respectfully traverses this rejection and submits that the subject invention is unobvious over the combination of Scolnick, Sabbagh and May. It should be understood that the primary reference of Scolnick is directed to the reduction of levels of ApoE 4 in the blood, and does not teach or suggest any relationship between ApoE 4 and Aβ in APP processing disorders. ApoE 4 is completely different gene product than Aβ. The failure of Scolnick to teach or suggest any application to Aβ is even acknowledged in the Office Action, wherein it states: "Scolnick do[es] not expressly disclose a method for treating a mammal having an APP processing disorder, lowering the amount of A-β peptide.....or plaque in the brain of the mammal by administering HMG-CoA reductase inhibitor." Therefore, the primary reference of Scolnick is deficient in its teaching of the claimed method, which concerns treatment of APP processing disorders by administering an HMG-CoA

reductase inhibitor. Moreover, Scolnick makes no connection between the reduction of ApoE 4 levels in the blood and APP processing disorders.

The secondary references of Sabbagh and May fail to cure this deficiency of Scolnick. Although both of these secondary references speculate that Aβ may relate to or be involved in Alzheimer's Disease, neither Sabbagh nor May provide a nexus to ApoE or HMG-CoA reductase inhibitors as described by Scolnick. Therefore, there is no motivation provided by any one of these references, for one skilled in the art to combine them, in asserting an obviousness rejection against the claimed invention.

Moreover, even assuming *arguendo* that the cited references are properly combined, they do not suggest or otherwise make obvious to a person of ordinary skill in the art, that the administration of a HMG-CoA reductase inhibitor can successfully be used for treating APP processing disorders. At best, the cited references, in combination, would make such treatment of APP processing disorders "obvious to try." Obvious to try is not the proper standard for asserting a §103 rejection. MPEP 2145 citing *In re O'Farrell* 853 F.2d at 903. Applicants therefore respectfully submit that a fair reading of the cited Scolnick, Sabbagh, and May references would not have made obvious to one skilled in the art, the subject invention as currently claimed. Accordingly, the references alone or in combination would not have suggested the claimed invention. Reconsideration and withdrawal of the rejection is, therefore, respectfully requested.

NO/

Claims 1-28 have further been rejected under 35 USC 103(a) as being unpatentable over Simons et al. The Office action asserts: "Simons et al. teaches that Lovastatin, a HMG-CoA reductase inhibitor, is useful in treating a mammal having an

APP processing disorder..." see Simons, et al., at p. 6461. Applicants believe this conclusion of the teaching of Simons may be an over generalization, in that Simons, et al. require more than one active agent, namely, methyl-β-cyclodextrin, mevalonate and lovastatin to achieve reduction in cholesterol. In fact, Simons et al utilize methyl-β-cyclodextrin in amounts that were previously known to reduce cholesterol. Moreover, there is no teaching or suggestion in Simons et al. that their results can be successfully achieved without the combination of methyl-β-cyclodextrin with lovastatin and mevalonate.

In accordance with the established tenet of patent law that an obviousness rejection cannot properly be asserted absent the teaching or suggestion founded within the prior art, applicant believe that Simons et al. does not support a rejection under 35 USC § 103(a).

Furthermore, applicants believe Simons et al. actually teach away from the claimed invention. For example, Simons et al. expressly state that lovastatin alone does not lower cholesterol or Aβ levels. (see Simons et. al, at pp. 6461 and 6462) MPEP 2141.02 states "[a] prior art reference must be considered in its entirety, i.e. as a whole, including portions that would lead away from the claimed invention." Simons et al. was published in 1998, more recently than either of Scolnick (1995), Sabbagh, (1997), or May (1997). Applicants contend that when read in its entirety, Simons et al. teaches that administration of HMG-CoA reductase inhibitors in combination with mevalonate, *in vitro*, did **not** have a significant effect on cholesterol reduction in cells, nor in the level of Aβ (pp. 6461-6462). Simons teaches or suggests that HMG-CoA reductase inhibitors in the presence of mevalonate, would **not** be useful in treatment of APP disorders without

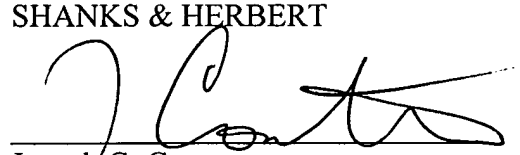
co-administration of methyl-β-cyclodextrin. It would, therefore, not have been obvious to one skilled in the art reading Simons et al. alone, nor in view of Scolnick, Sabbagh or May, to systemically administer HMG-CoA reductase inhibitors alone to a mammal (*in vivo*) and anticipate any reduction in the levels of Aβ. Accordingly, the cited art neither anticipates nor renders obvious any of the Applicants' claims. Reconsideration and withdrawal of the rejection on these grounds is, therefore, respectfully requested.

Applicants believe that the subject invention as now claimed is patentable over the cited references. Accordingly, applicants respectfully request that the rejection under 35 USC §103(a) be withdrawn upon reconsideration.

Based upon the foregoing amendments and representations, applicants submit that the rejection of the claims in the above-identified application have been overcome and should be withdrawn. Early and favorable action is earnestly solicited.

It is believed that a 3-month extension of time is required, however, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 CFR §1.136(a), and any fees required therefore are hereby authorized to be charged to Deposit Account No. **50-0622**, referencing Attorney Docket No. **0200-0004**.

Respectfully submitted,
SHANKS & HERBERT



Joseph G. Contrera
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February 15, 2001

Ted Whitlock, Esq.
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Re: U.S. Patent Application
App. No: 09/704,554 Filed: November 3, 2000
For: Method of Treating Amyloid ß Precursor Disorders
Inventors: Friedhoff
Our Ref: 0200-0004US

Dear Ted:

We are pleased to report the filing of the following documents in the United States Patent and Trademark Office:

1. Amendment Cover Sheet
2. Preliminary Amendment;
3. Our Check in the amount of $114.00; and
4. Return postcard.

Copies of these documents are enclosed for your records.

We will keep you informed of any further developments in this case. If you have any questions, please do not hesitate to contact us.

Sincerely,

Suzannah K. Sundby*

*Member of the California bar, a bar other than Virginia.

Enclosures

SKS/lb

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In re application of: Friedhoff, et al.

Atty. Docket No. 0200-0004

Appl. No.: 09/704,554
Filed: November 3, 2000
For: Method of Treating Amyloid β Precursor

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:
Transmitted herewith is an amendment in the above-identified application.

- ☐ Small entity status of this application under 37 C.F.R. §§ 1.9 and 1.27 has been established by a verified statement previously submitted.
- ☐ A verified statement to establish small entity status under 37 C.F.R. §§ 1.9 and 1.27 is enclosed.
- ☐ No additional fee is required.

The fee has been calculated as shown below:

	(Col. 1) Claims Remaining After Amendment		(Col. 2) Highest No. Previously Paid For	(Col. 3) Extra	SMALL ENTITY Rate	Fee	or	LARGE Rate	Fee
Total	35	minus	33	2	x 9 =	$	or	x 18 =	$36
Indep.	8	minus	7	1	x 39 =	$	or	x 78 =	$78
☐ **First Presentation of Multiple Dependent Claims**					+ 130 =	$	or	+ 260 =	$
					Total	$	or	**Total**	$114.00

* If the entry in Col. 1 is less than the entry in Col. 2, write "0" in Col. 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, write "20" in this space.
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, write "3" in this space. The "Highest Number Previously Paid For" (Total or Independent) is the highest number found from the equivalent box in Col. 1 of a prior amendment or the number of claims originally filed.

- ☐ Please charge Deposit Account No. _____ in the amount of $_____. A duplicate copy of this sheet is attached.
- ☒ A check in the amount of $ 114.00 is enclosed.
- ☐ The U.S. Patent and Trademark Office is hereby authorized to charge payment of the following fees associated with this communication or credit any overpayment to Deposit Account No. _____. A duplicate copy of this sheet is attached.
  - ☐ Any filing fees under 37 C.F.R. § 1.16 for the presentation of extra claims.
  - ☐ Any patent application processing fees under 37 C.F.R. § 1.17.

Respectfully submitted,

SHANKS & HERBERT

Suzannah K. Sundby
Reg. No. 43,172

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Friedhoff, et al.

Serial No. 09/704,554

Filed: November 3, 2000

For: Method of Treating Amyloid ß Precursor Disorders

Art Unit: Not Assigned

Examiner: Not Assigned

Atty. Docket: 0200-0004

SECOND PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to examination of the above-identified application, Applicants herewith respectfully request the following amendments:

IN THE CLAIMS:

Please add the following new claims:

--34. (New) A method of treating, preventing or inhibiting the progression of Alzheimer's disease in a mammal comprising administering to the mammal a controlled release composition comprising a therapeutically effective amount of at least one HMG-CoA reductase inhibitor.

35. (New) The method of claim 34, wherein the HMG-CoA reductase inhibitor is mevastatin, pravastatin, simvastatin, atorvastatin, lovastatin, rivastatin, fluvastatin, or a pharmaceutically acceptable salt, isomer or active metabolite thereof.--

Remarks

Support may be found in the specification generally. Accordingly, no new matter has been added and entry of this amendment is respectfully requested.

It is respectfully requested that the Examiner enter these amendments prior to examining the application on its merits.

Respectfully submitted,

SHANKS & HERBERT

By: _____

Suzannah K. Sundby
Reg. No. 43,172

Date: 14 February 2001

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Applicant: Lawrence Friedhoff, Joseph Buxbaum
App. Serial No: 09/704,554
Filed: November 3, 2000
For: Method of Treating Amyloid β Precursor Disorders

Docket No.: 0200-0004
By: ~~Suzannah K. Sundby~~
Shanks & Herbert

When receipt stamp is placed hereon, the USPTO acknowledges receipt of the following:

1. Amendment Cover Sheet
2. Preliminary Amendment;
3. Our Check in the amount of $114.00; and
4. Return postcard.